

*University of Baghdad*  
*College of Veterinary Medicine*  
*Department of Physiology and Pharmacology*

## **Lecture- 3**

# **Neuromuscular Junction and Muscle Physiology**

**For Class- Two**

**By**

**Professor**

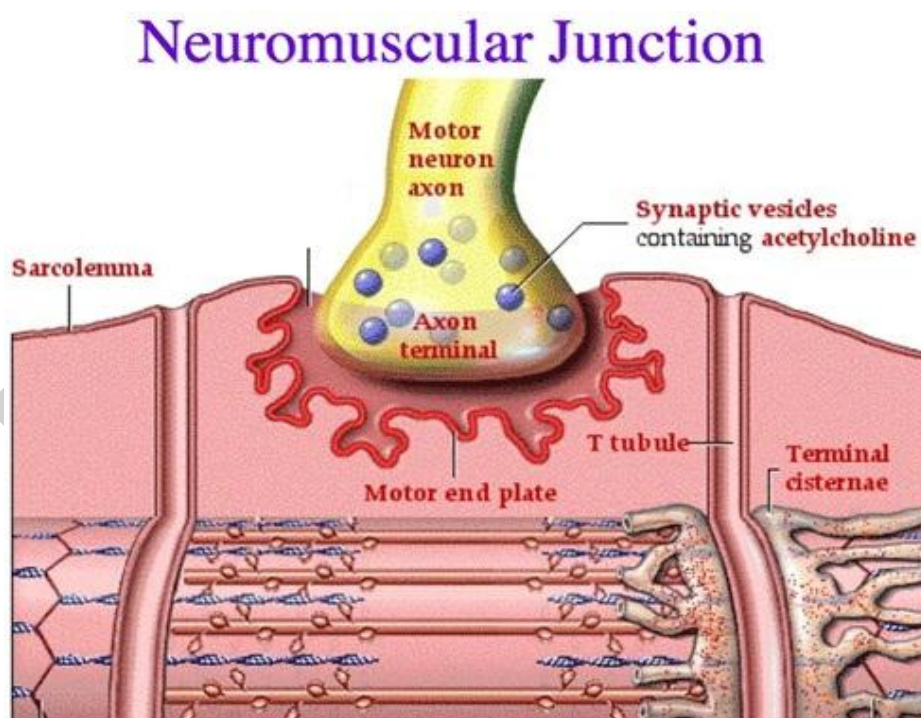
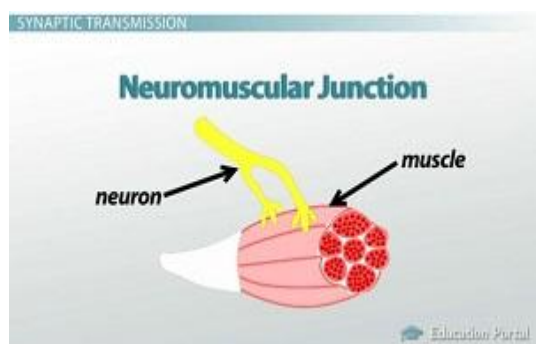
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## The Neuromuscular Junction ( or Myoneural Junction)

**Neuromuscular junction**, is a chemical synapse formed by the contact between nerve ending of large myelinated motor neuron and skeletal muscle fibers, at the midpoint of muscle fibers, so the action potential produced in muscle fiber can travels in both directions toward the muscle fiber ends.

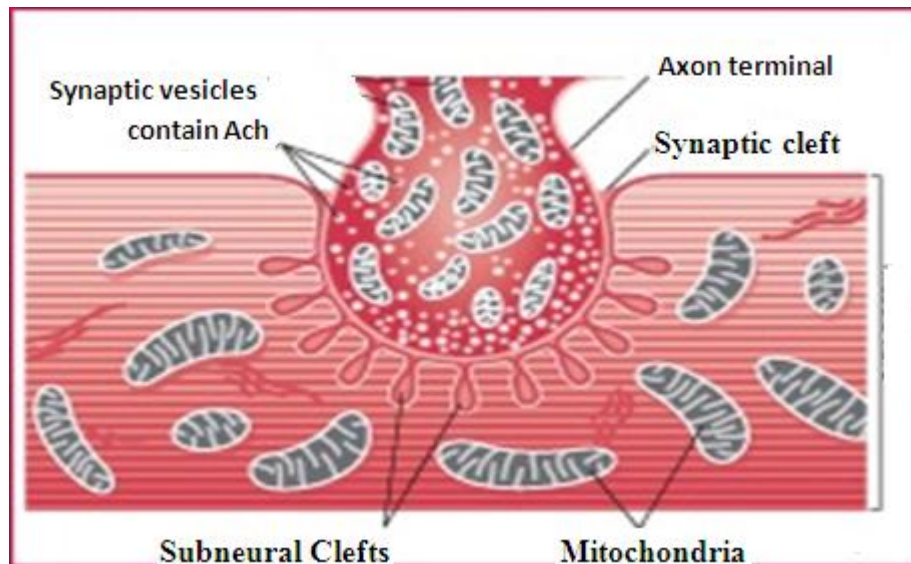
The junction between motor neuron and skeletal muscle fibers formed a thickened muscle surface area called "**the motor end plate**".



**The neuromuscular junctions include :**

- Presynaptic nerve endings ( motor nerve terminal).
- **synaptic cleft** : is the space between terminal of motor nerve and membrane of muscle.
- **Synaptic Gutter**: it is the invaginated sarcolemma of muscle fibers, its contain a large numbers of acetylcholine receptors called "**nicotinic receptors**".
- **Subneural Clefts**: these are small folds of the muscle membrane present at the bottom of the synaptic gutter to increase the surface area, as well as, contain a large quantities of the enzyme called "**acetylcholinesterase**".

**Note:** The motor nerve endings contain mitochondria that supply ATP used for synthesis of Ach.



### Sequence of events during stimulation of neuromuscular junction:

- Stimulation of motor nerve caused an initiation of action potential and caused opening of voltage-gated calcium ion channels at the nerve endings leading to release of **ACh** into the synaptic cleft by exocytosis ( **as described previously** ).
- ACh will diffuse into the synaptic cleft and binds with special receptors on muscle membrane , called **nicotinic receptors** , causing a rapid influx of  $\text{Na}^+$  ions into the muscle membrane resulting to generation of local depolarization called **end plate potential (EPP)**.
- **The EPP** is responsible for firing of an **action potential** of muscle membrane, then action potential will be spread through all of the muscle membrane fibers causing an excitation of skeletal muscle fibers followed by contraction as illustrated in the following figure:

### The Neuromuscular Junction

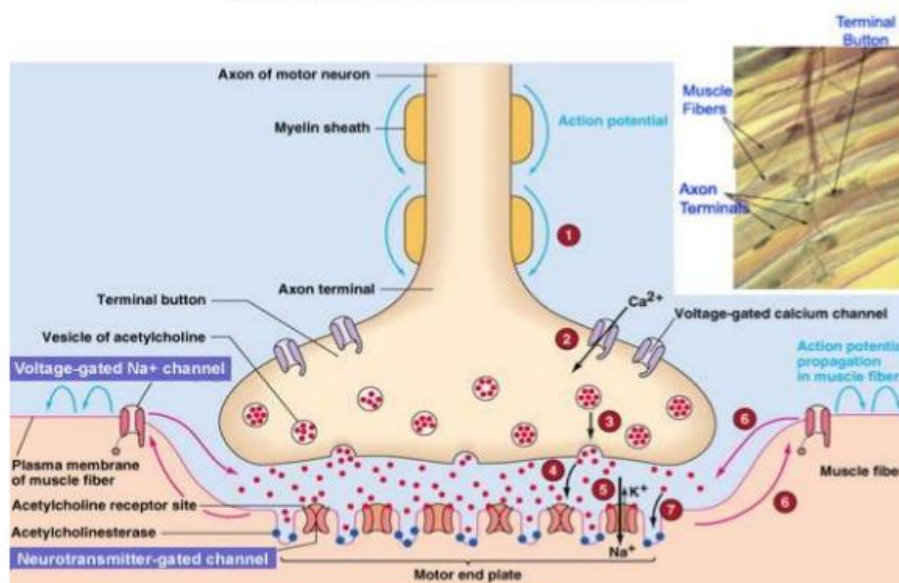


Figure: Sequence of events during stimulation of neuromuscular junction

**Note:**

- Curare, is a poisoning that binds to **nicotinic receptors** causing **block** these receptors. (which used by the American Indians to paralysis of victims).
- Strychnine is a highly toxic substance, an "**acetylcholinesterase inhibitor**", that inhibits the breaking down of acetylcholine by the acetylcholinesterase enzyme.

## Muscle Physiology

### Main functions of Muscles:

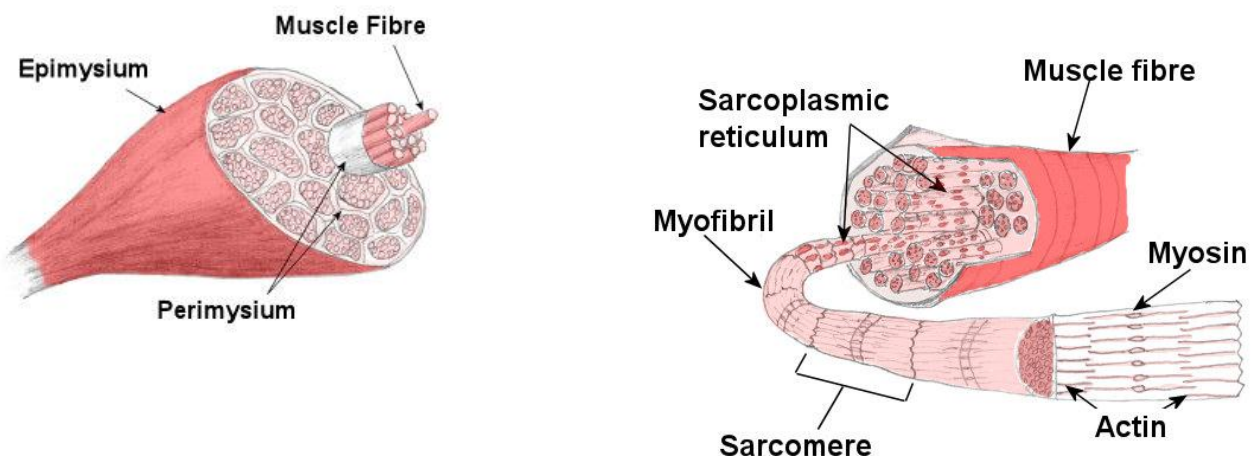
1. Locomotion and maintenance of posture ( contraction of skeletal muscle).
2. Vasoconstriction and vasodilatation of blood vessel walls ( smooth muscles) .
3. Peristalsis, that is a wave like motion along the digestive tract (smooth muscles).
4. Cardiac muscle (heart) contractility and relaxation.

### Types of muscles:

#### I- Skeletal muscles:

##### Functional morphology of Skeletal muscles

- It is striated, under voluntary control and multinucleated (several nuclei per cell ).
- Sarcoplasmic reticulum is well developed (contain high concentration of  $\text{Ca}^{+2}$  ions ).
- Transverse tubule ( T tubule ) well developed to transport calcium.
- Skeletal muscle is made up of **muscle fibers**, is a single muscle cell.
- The cell membrane of muscle fiber is called "**sarcolemma**" and the cytoplasm is called "**sarcoplasm**".
- The sarcoplasm contains abundant , parallel thread like **fibers** called "**myofibrils**".
- The myofibrils are divisible into individual **filaments** ,composed of muscle proteins elements including: **contractile and regulatory proteins**.
- Myofibrils are composed of repeating sections area called "**sarcomere**".



## Sarcomere:

is the basic functional unit of striated muscle tissue, which is an area between two Z lines, so give skeletal muscles their striated appearance. Sarcomeres are composed of long fibrous proteins elements as filaments, that slide on each other when a muscle contracts or relaxes.

### Striation pattern of skeletal muscles including:

- **I bands** (the light bands), is composed of thin filaments (**actin filaments**).
- **A bands** (the dark bands), is composed of thick and thin filaments.
- **H zone**, is the region that the thin filaments (actin) failed to overlap the thick filaments (myosin).

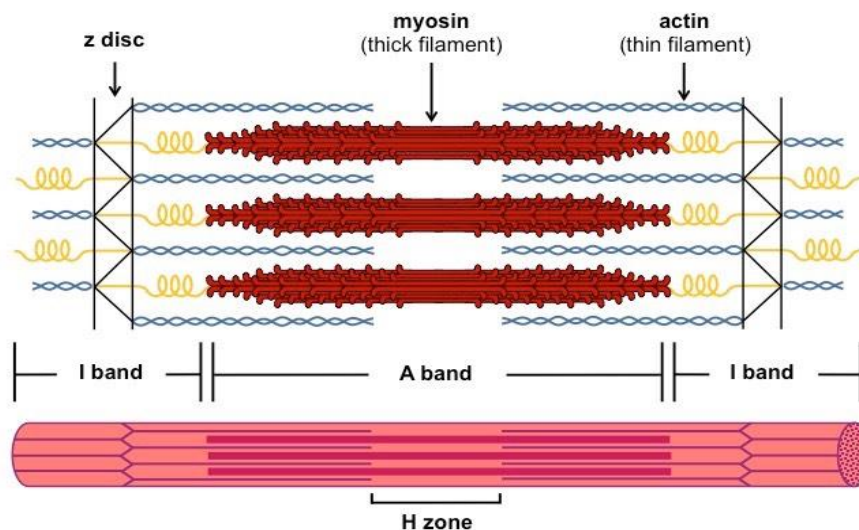


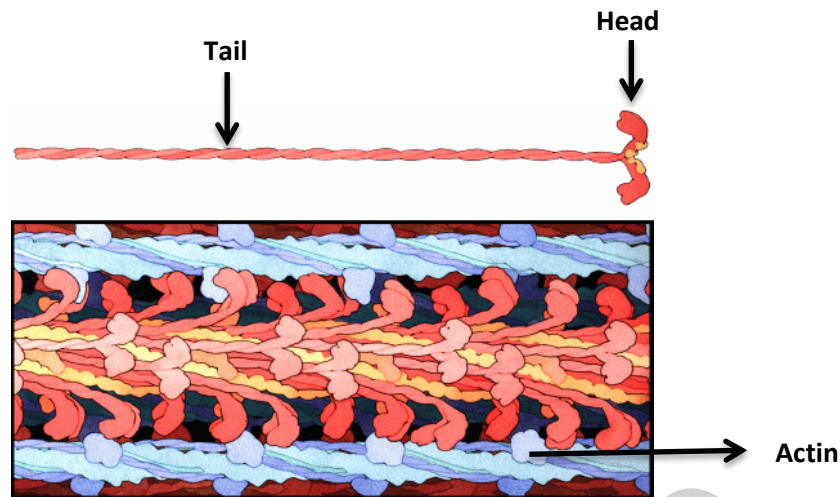
Figure: Structure of a Sarcomere

## The muscle proteins:

There are two main types of muscle proteins including

### A- Contractile proteins including:

1. **Actin** , is a globular protein, contain an active sites to which the heads of the thick filaments (myosin) attach.
2. **Myosin** , is a thick filament of an elongated protein composed of **double tails** and **two heads** ,with shaped like golf clubs with long shaft.



**Structure of myosin and actin**

#### **B- Regulatory proteins including:**

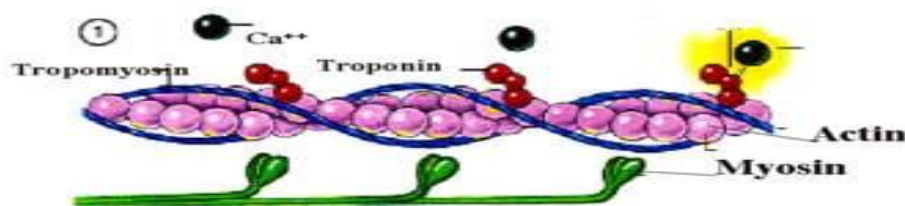
1. **Tropomyosin** , is an actin binding protein, it is a coiled shape, that helps to support the actin filaments.
2. **Troponin (or Troponin complex)**, is attached to the protein tropomyosin , that is necessary to muscle contraction in skeletal muscle and cardiac muscle, but not in smooth muscle.

Troponin is composed of three regulatory subunits proteins including :

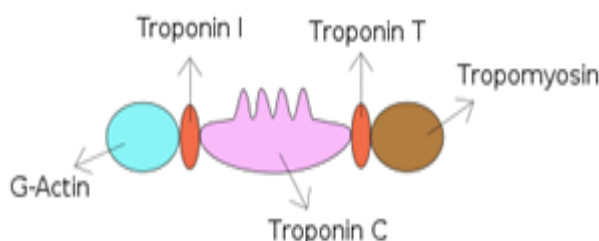
**Troponin-T (Tn-T):** binds to tropomyosin subunit to form a troponin-tropomyosin complex.

**Troponin-C (Tn-C) :** is a  $\text{Ca}^{+2}$  binding subunit, when binds to  $\text{Ca}^{+2}$  produce conformational changes in **Tn-I** for regulation of muscle contraction.

**Troponin-I (Tn-I) :** this subunit covered the active binding site of actin thin filaments during muscle relax .



**In relaxed muscle** , myosin cannot bind to actin. Whereas, during **contraction**,  $\text{Ca}^{+2}$  binds to the **Tn-C** causes a conformational changes which lead to **Tn-I** leave the active binding sites on actin filaments , and thereby leading to binding of actin to the head of myosin.



**Subunits of troponin during relaxation**

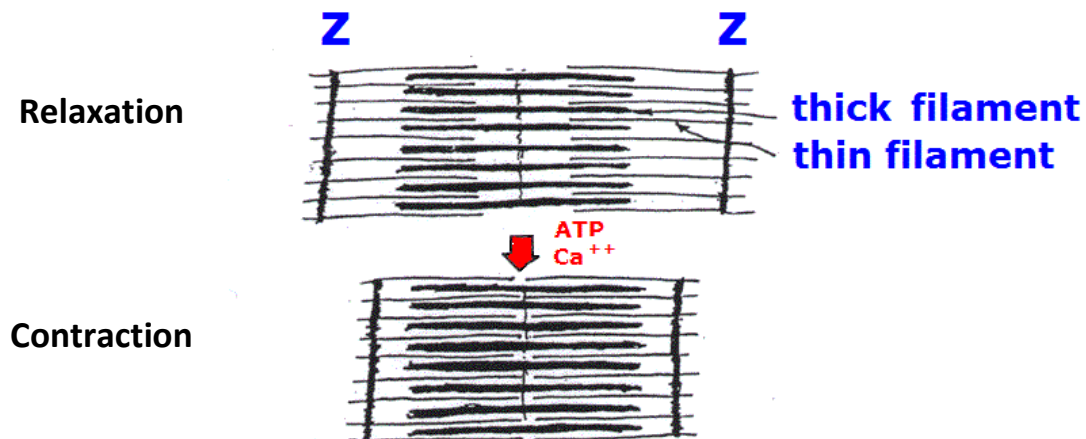
### **Sequence of events of skeletal muscle contraction :**

1. Stimulation of motor nerve produce an action potential which cause release of acetylcholine (**Ach**) at nerve endings into the synaptic cleft by exocytosis, and binds with **nicotinic receptors** on the membrane of the skeletal muscle fibers.
2. Binding of **Ach** with **nicotinic receptors**, will allow the opening of  $\text{Na}^+$  ions channels, which in turn led to the **influx of  $\text{Na}^+$**  ions inside the muscle fibers.
3. Increase concentration of  $\text{Na}^+$  within the muscle cells , cause initiation of end plate potential (**EPP**) on muscle membrane leading to start generation of depolarization that is responsible to rising an action potential
4. The action potential spreads throughout the membrane of the muscle fiber, and especially within the **T-tubules** of the muscle fiber, causing depolarization of sarcoplasmic reticulum (**SR**) , which promotes release of  $\text{Ca}^{+2}$  ions from **SR** by simple diffusion.
5. The free  $\text{Ca}^{+2}$  binds with the **Tn-C** causes the conformational change of the **Tn-C**.
6. Presence of  $\text{Ca}^{+2}$  with **ATP** that allows to formation of **cross-bridge** between actin and myosin causing sliding of thin filaments on thick filaments followed by **shortening** of muscle fiber (**i.e.** contraction of muscle according to **Sliding Muscle Theory** .

## Sequences of events of skeletal muscle relaxation :

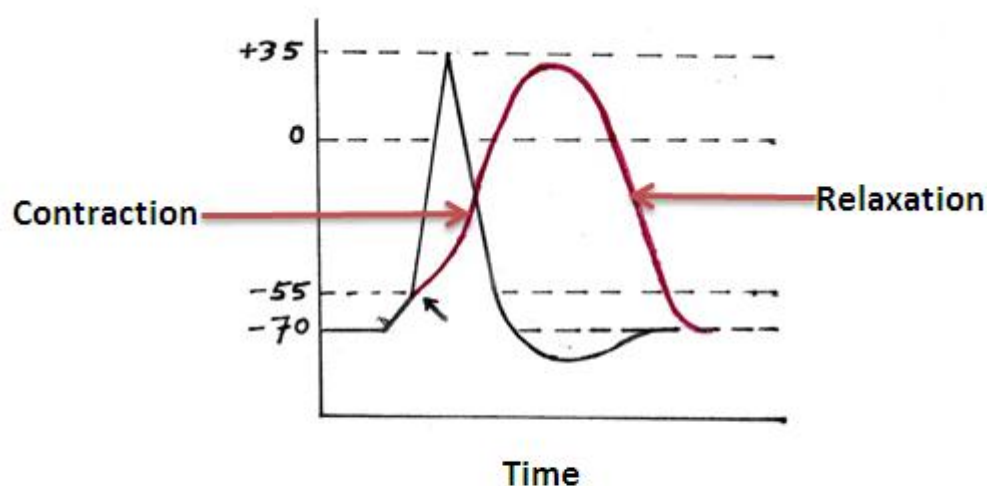
Muscle relaxation occur when:

- Cessation of stimulation of motor nerve .
- Cessation release of  $\text{Ca}^{+2}$  from sarcoplasmic reticulum.
- Release of  $\text{Ca}^{+2}$  from **Tn-C** subunits.
- $\text{Ca}^{+2}$  pumped back ( or reuptake) actively into the sarcoplasmic reticulum .
- Cessation of interaction between actin and myosin and the muscle relaxes.



## Excitation-contraction coupling in skeletal muscle:

It is the sequence of events through which the nerve fiber stimulates the skeletal muscle fiber ( an electrical events ) followed by contraction ( a mechanical events) as illustrated in the following diagram :



Excitation-contraction coupling of skeletal muscle

# Cardiac Muscle

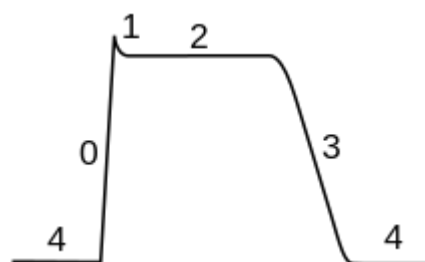
## Functional morphology of cardiac muscle

- It is under involuntary control.
- It is striated as in skeletal muscle.
- Each cardiomyocyte contain one or two large nuclei per cardiomyocytes.
- Sarcoplasmic reticulum are well developed.
- Cardiac muscle is made up of **muscle fibers**, branched and connected with each other's by an **intercalated discs**, which act as gap junctions, that is very permeable for diffusion of ions.
- The heart muscle thus acts as a **syncytium**(. i.e. a multinucleated mass). Therefore, when one of the cells is excited, the action potential spreads fast from one cell to other cells and a whole muscle contracted.

## Action Potential of Cardiac Muscle:

- The cardiac action potential is a change in membrane potential across the cell membrane of cardiomyocytes.
- The cardiac action potential arises (or initiated) from a group of cells located in the wall of the right atrium called the **Sinoatrial node (SA node )**. These cells have the ability to spontaneously produce of an action potential that travel through the heart causing it to contract.

## Phases of the cardiac action potential



### Phase 4 :

Phase 4 occur when ventricular myocytes is at in resting membrane potential, in a period known as " **diastole** ".

### Phase 0 ( depolarization phase ):

In this phase a rapid fast increase in the permeability of cell membrane of **SA-node** and ventricular cells to  $\text{Na}^+$  (i.e. **increase  $\text{Na}^+$  influx** ). This phase lasting less than **2 ms**.

### **Phase -1: Initial rapid repolarization**

This phase begins with the rapid **close** of the  $\text{Na}^+$  channels, at the same time  $\text{K}^+$  channels **opening and closure rapidly**, allowing for flow of  $\text{K}^+$  ions outside of the cell.

### **Phase -2: Plateau phase**

Plateau phase occur due to slow opening of  $\text{Ca}^{+2}$  channels, with activation of chloride channels. This phase is responsible of the large duration of the action potential.

### **Phase 3: Late rapid repolarization :**

In this phase,  $\text{Ca}^{+2}$  channels close while the  $\text{K}^+$  channels slow opening causing more  $\text{K}^+$  leak outside the cells (**i.e. increase  $\text{K}^+$  efflux** )

## **Smooth Muscles**

### **Functional morphology of smooth muscles**

- It is under involuntary movements, such as the peristalsis contractions in the esophagus, stomach and intestine.
- Smooth muscle cells it is non-striated muscles, its elongated spindle-shaped cells with greater elasticity.
- Actin, myosin and tropomyosin are present in smooth muscles.
- Smooth muscle does not contain the protein **troponin**; instead contain a protein called "**calmodulin**".
- Sarcoplasmic reticulum is poorly developed.
- Its contain a few mitochondria, and depends on glycolysis in their metabolism.

### **Excitation of smooth muscle**

- A smooth muscle is excited by stimuli, which causes spontaneously contraction, as well as relaxation, their induced by a number of physiochemical agents (e.g., hormones, drugs and neurotransmitters).
- The resting membrane potential is **instability** with the value about **-50mv**.
- In smooth muscle, **Slow waves** cause no smooth muscle contraction, but when the **slow-wave** reached the **threshold** before contraction.

- **slow-wave threshold** cause activation of  $\text{Ca}^{+2}$  channels, resulting in binding of  $\text{Ca}^{+2}$  to calmodulin caused an initiation of motility.

### **Smooth muscles divided into two subgroups :**

- **Single-unit** smooth muscles (unitary) : this type most common present in blood vessels , urinary tract and the digestive tract.
- **Multiunit smooth muscle:** this type present in the trachea, large elastic arteries, and the iris of the eye.